



Role of Co Q-10 in Copper Sulphate Toxicity in Chick's Model

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OUR aim was to investigate the ability of coenzyme Q-10 to counteract the damage caused by copper sulphate poisoning, at the nervous system pharmacological challenge levels, oxidative stress and, some biochemical parameters, as well as study of histopathological changes in the brain. In this experiment, 72 chicks were randomly divided into 6 groups of 12 chicks each. Only distilled water was administered to the G1 control group. Copper sulphate alone at a dose of 19.5 mg/kg was given to the G2 group. The G3 group was given 30 mg/kg of CO Q-10 alone for 7 days. The G4 group was given copper sulphate for 3 days and Q-10 for 7 days. The G5 group was given copper sulphate for 3 days before receiving CoQ-10 for 7 days. The G6 group was given coenzyme Q-10 alone for 7 days before being given copper sulphate for 3 days. The pharmacological challenge revealed substantial differences in the onset of sleep and sleep duration in chicks given co-enzyme Q-10 with copper sulphate at various times. Total oxidative stress, glutathione, and malondialdehyde in serum and brain tissue were also linked to an increase in Caspase-3 activity in brain tissue, while groups that received coenzyme Q-10 with copper sulphate concurrently or prior to oxidative stress had less oxidative stress and less histopathological changes in brain tissue. We concluded that giving the Co Q-10 at the same time as or before copper sulphate lowered the toxicity of copper sulphate. Some oxidative stress markers, as well as biochemical indicators, histopathological abnormalities, and programmed cell death in brain cells, were used to demonstrate this.

Keywords: Coenzyme Q-10, Copper Sulfate, Oxidative stress, Caspase-3, Chicks

Introduction

Coenzyme Q10 or Co Q-10, also known as ubiquinone, is a proton and electron carrier mobile in the mitochondrial respiratory chain with antioxidant capabilities. It is widely utilized as an antioxidant and to alleviate the symptoms of a variety of diseases. Coenzyme Q-10 functions as an electron transporter in mitochondria, facilitating electron transfer. Its reduced form, ubiquinol, also functions as an antioxidant in cell membranes and organelles [1,2]

Ubiquinone protects against the potentially harmful effects of free radicals generated during mitochondrial inner membrane phosphorylation

and oxidative stress, which causes glutathione loss and DNA and oxidized protein damage, and plays a role in several neurodegenerative disorders in humans, including Alzheimer's disease and Parkinson's disease [3,4].

Coenzyme Q10 has a long history in medicine, with applications spanning from neurological illnesses like multiple system atrophy (MSA) to conditions like Barth syndrome, heart failure, fibromyalgia, and insulin resistance [5].

Inorganic copper is absorbed directly into the bloodstream and can pass the blood-brain barrier. Despite the fact that copper is attached to protein, it can uncouple from it and release it, catalyzing the

creation of highly reactive hydroxyl free radicals and other reactive oxygen species (ROS) [5,6].

Copper can cause oxidative damage in cell culture, interfering with important cellular events such as protein components required for neuronal function, and disruptions in copper homeostasis can lead to copper metabolism problems and disorders associated with new degenerative changes [7].

The goal of this study was to see if coenzyme Q-10 might protect the brain from copper sulphate poisoning, at the pharmacological challenge levels, oxidative stress, and several metabolic indicators, as well as histological abnormalities.

Materials and Methods

Animals

Local chickens of both sexes were employed in this investigation, with 72 chicks hatched in the animal house of the College of the Veterinary Medicine University of Mosul. The chicks were obtained from local hatcheries, and the experiment began at the age of seven days, the chicks weighed between 225 and 250 g. Chicks are housed in special cages with plenty of water and food, with specific attention paid to breeding factors such as light, nutrition, and temperature. Ethics in dealing with animals and humane care of them were followed.

Ethical approval

The University of Mosul's College of Veterinary Medicine approved all of the techniques utilized in this investigation. Committee on Animal Ethics (Iraq)

Medicines and chemicals

Copper sulphate is a type of copper salt. Karlsruhe, Germany Zeppelinstrassa. Coenzyme Q-10 from Scharlau in Spain, TAC from TEDA in England, TBA from Merck, 0.25 N HCl, 10% buffer DTNB, L-Glutathione, TCB, Na₂HPO₄ buffer, formalin 10%

Glutathione standard concentrations are 0.0003125 – 0.10 mg / 0.5 ml, the diagnostic kit Caspase-3 and TAC (total antioxidant capacity) kit from Elabscinse, USA.

Dose preparation

After estimating the specific dose for each chemical, doses of copper sulphate and Q-10 were prepared and dissolved in distilled water, then administered to the animals through an oral dosing syringe.

Blood sample collection

The chicks' jugular veins were cut in order to collect blood in special tubes. After collecting the blood samples, they were centrifuged for 15 minutes at 3000 rpm. The plasma and serum samples were maintained frozen at -20°C in special plastic tubes until laboratory biochemical analyses were done.

Organ extraction

After the chicks were slaughtered, the skulls were opened and the entire brains were taken. Each sample was divided into sections and placed in numbered bags in the freezer at -20°C. The remaining section of each sample was placed in special containers containing formalin at a 10% for preservation until the histological investigation, taking into account the numbering of each group separately. The livers were removed, rinsed in plain water, then placed in special numbered bags and preserved in the freezer at -20 °C until the laboratory analysis.

Experiments

The effect of administering co-enzyme Q-10 with copper sulphate at different intervals on the pharmacological challenge with ketamine and xylazine anaesthesia in chicks is being investigated.

In this experiment, 72 chicks were randomly assigned to 6 groups of 12 chicks, each aged 7 days and treated with copper sulphate at a dose of 19.5 mg/kg during 3 days. The dose was calculated based on the results of the preliminary tests and is as follows: G1 only distilled water was given to the control group. G2: Copper sulphate group alone (19.5 mg/kg). G3: Coenzyme Q-10 30 mg/kg for 7 days on its own. G4: Copper sulphate treatment for 3 days and Q-10 treatment for 7 days. G5: Copper sulphate treatment for 3 days, then Q-10 treatment for 7 days. G6: For 7 days, the group was given only coenzyme Q-10, then 3 days of copper sulphate.

Following the completion of the treatment period in the experiment, six chicks from each group are tested in a pharmacological challenge test, and another six are slaughtered for blood collection for biochemical measures.

Pharmacological challenge experience

The chicks were conducted a pharmacological challenge test with xylazine 5 mg/kg injected subcutaneously and ketamine 20 mg/kg injected into the chest muscle after the previous treatments were completed.

Biochemical Measurement

1-The total antioxidant Capacity (TAC) in brain tissue and plasma were all (TAC) measured with a specialized measuring kit.

2- Glutathione concentration in the serum:

The concentration of glutathione in serum was determined using the modified Elman technique [8].

3 - Determining the level of malondialdehyde (MDA) in the serum:

The MDA-TBA2 combination is formed when malondialdehyde and thiobarbituric acid interact to generate the MDA-TBA2 complex, which is absorbed in 352 nm [9].

4 - Assessing CASPASE-3 activity in liver and brain tissue.

The researchers employed a specialized measuring kit from Elabscinse, America.

Statistical analysis

Parametric data were statistically evaluated using the statistical programme spss (ANOVA test), and then the least significant difference (LSD) test was applied at a probability level of less than $p < 0.05$.

Results

Experience of pharmaceutical challenges

When compared to the control group and copper sulphate group, chicks treated with copper sulphate had a significant drop in the period of onset of sleep with a decrease in the duration of anaesthesia. While the rest of the

groups had a substantial increase in the period of onset of sleep in groups treated with CoQ10 facilities alone or with copper sulphate. In terms of sleep duration,

When compared to the control group and the copper sulphate group, the groups treated with the COQ10 alone or with copper sulphate recorded a significant marked decline in the chicks' sleep duration, and the enzymatic COQ10 group recorded a significant decrease in the onset of sleep and a decrease in the duration of sleep. In comparison to the control group and the other groups (Table 1).

The experiment of biochemical variables

The total antioxidant capacity, glutathione, and malondialdehyde in the serum and brain tissue of chicks were measured to determine the level of oxidative stress.

The group treated with copper sulphate alone had a significant decrease in total antioxidant capacity in brain tissue and plasma when compared to the Q-10 group alone and the copper sulphate group with Q-10. The group Q-10 alone had a significant increase than the control group, while the group treated with copper sulphate before Q -10 had a significant decrease compared to the Q-10 group alone and the copper sulphate group with Q-10. there was no significant difference between the copper sulphate after Q-10 group and the control group and the other groups (Table 2).

TABLE 1. Effects of xylazine and ketamine anaesthetics on various periods of copper sulphate and Q-10 treatments in chicks.

Parameters	Beginning to sleep/sec	Length of sleep/min
Control	180± 65	200±39
CuSO ₄	80 ±25*	170± 35*
CO Q-10	200± 45 a*	90±15 a*
CuSO ₄ with Q-10	20535± a*	146± 17 ^{ab*}
CuSO ₄ before Q-10	25± 20 a*	130± 35 ^{ab*}
CuSO ₄ after Q-10	200 ±65 a*	145±33 ^{ab*}

Each group consisted of 6 animals, and the data were averaged ± standard error.* Represents the significant difference from the control group at $p < 0.05$

a represents a significant difference from the copper sulphate group

b represents a significant difference for the CO Q-10 group

When compared to the control and copper sulphate groups, the group treated with copper sulphate alone had a significant decrease in glutathione and a significant increase in malondialdehyde in the serum. While the group treated with Q-10 alone had a significant increase in glutathione and a decrease in malondialdehyde. While the group treated with copper sulphate before Q-10 had a significant decrease in glutathione and a rise in After Q-10, the copper sulphate group had a significantly lower glutathione level than the Q-10 group alone, but no significant difference from the control group (Table 2).

Measurement of caspase-3 activity in brain tissue and liver

The results showed that there was a significant increase in caspase-3 activity in the groups treated with copper sulphate alone before or after treatment with the coenzyme Q-10, while no significant difference in caspase-3 activity was recorded in the group treated with coenzyme Q-10 alone or with copper sulphate at the same time (Table 3).

Study the histopathological changes of the brain.

Treatments with varying periods of copper sulphate and coenzyme Q-10 resulted in histopathological alterations.

The results of the histopathological study appeared in Figures 1 and 2, the normal structure of the brain tissue. As well as in Figures 3 and 4, the brain tissue of a chick from the group treated with copper sulfate with coenzyme Q10 showed the cerebral cortex, in which the normal histological structure of neurons and glial cells, with slight perivascular edema and periaxonal axons edema and figures 5 and 6 of two histological sections of the brains of the group treated with copper sulfate and then coenzyme Q10, showed the cerebral cortex, which has an increase and accumulation of glial cells, diffuse perivascular, periaxial edema and vacuolization of glial cells. Neurons, glial cells, and blood vessels (Figs. 7 and 8). The group treated with coenzyme Q10 and then copper sulfate showed that the cerebral cortex had a normal histological structure of neurons with mild perivascular and periaxonal edema (Fig. 9 and 10).

Discussion

The aim of giving coenzyme Q-10 to chicks treated with copper sulphate at different times was to see if the antioxidant coenzyme could protect the phospholipids membrane and mitochondrial membrane from oxidative damage caused by

copper sulphate, as copper sulphate stimulates free radical formation by increasing the concentration of copper above what the cell requires [10,11].

One of the strategies used to seek the latent or hidden effects of chemicals or poisons on the function of the central nervous system is the pharmacological or toxicological challenge [12, 13]. These changes could be changes in the central nervous system's physiological and biochemical functions, or they could show up in the animal on the A difference in behavioural manifestations and the pharmacological challenge shows the nervous system imbalance that was covered by the brain's adaptive mechanisms [14, 15].

The central nervous system's norepinephrine and dopamine neurotransmission is reduced by xylazine. It accomplishes this by attaching to the presynaptic surface of autoreceptors in the same way that norepinephrine does, so suppressing feedback [16].

Copper sulphate modulated the response to general anaesthesia in chicks and reduced the binding of ketamine to N-Methyl-D-aspartate receptors, and co-enzyme Q-10 seemed to have a predominant effect on all co-treatments with Copper sulphate, as the delay in the onset of sleep continued with a decrease in sleep time in these groups, and such results require a careful study of the kinetics of these drugs. Ketamine, which was converted into shorter and less potent anaesthetics in treated chicks, as well as the enzymatic conjugate, may influence drug metabolism and energy consumption in these animals.

Our research found that providing the Co-Q10 helper after copper sulphate treatment did not provide adequate protection against copper sulphate damage, resulting in irreversible damage during the Co enzymatic treatment time. Copper sulphate also produces free radicals and reactive oxygen species, which target the lipids and proteins in the body. Nucleic acids in the cell may be harmed by oxidative stress because mitochondrial DNA is more sensitive to future damage, and any mitochondrial dysfunction can result in permanent gene alterations. As a result, oxidative damage has the potential to generate long-term changes in how energy is produced, which can lead to apoptosis, as evidenced by our findings.

Increased formation of reactive oxygen species (ROS) and oxidative damage caused by changes in copper content are involved in neurodegenerative

processes, notably in the central nervous system [17,18].

Our findings showed that copper sulphate activates caspase-3, a protein produced by the CASP3 gene that interacts with caspase-8 and caspase-9. The implementation phase of apoptosis is dominated by caspase sequential activation. They are dormant main enzymes that are processed by proteolytic enzymes. Caspases 6 and 7 activate caspase-3. In Alzheimer's disease, the dominant caspase-3 is implicated in the breakdown of amyloid-beta protein, which is linked to neuronal death [19, 20].

Our findings support the hypothesis that copper sulphate increases caspase-3 activation, resulting in random cell death and an increase in oxidative stress, cascading

apoptosis, autophagy, and mitochondrial disruption, all of which contribute to cellular damage. CO Q-10, on the other hand, reduced the occurrences of programmed death, as evidenced by lower caspase-3 activity when given at same time with copper sulphate. CoQ10 has a role in neuroprotection due to the mechanism of inhibition of microglia, and has an anti-inflammatory effect by inhibiting the expression of Interleukin-6 (IL-6) and Tumor Necrosis factor (TNF), which cause apoptosis and neurodegeneration [21]. May be for all of above reasons the histopathological analysis also revealed that the application of copper sulphate prior to the CO Q10 generated harmful histological indications in the brain tissue while the harmful effect is reduced when they were given at the same time or after CO Q10.

TABLE 2. Oxidative stress status in different treatments with copper sulphate and Q-10 in chicks.

Parameters	Plasma TAC U/ml	Brain Tissue TAC U/ml	GSH in serum nmol/ml	MDA in serum nmol/ml
Control	36.5±3	4.1±1	0.05±0.001	2.29±1
CuSO ₄	23.7±2 ^{*bc}	1.0±0.1 ^{*bc}	*0.02±0.001	*4.29±1
CO Q-10	37.8±2	5.9±0.1 [*]	0.06 ± 0.001 ± ^{*a}	1±0.5 ^{a*}
Q-10 with CuSO ₄	33.9±3	3.2±1	0.001 ±3 0.0	1 ±13.2 ^a
Q-10 before CuSO ₄	23.7±3 ^{*bc}	0.9±0.01 ^{*bc}	0.09±0.01 ^{*b}	3± 0.01 ^{b*}
CuSO ₄ after Q-10	32.2±4	3.0±0.1 ^a	0.035 ± 0.008 ^b	2.81± 0.06 ^a

Each group consisted of 6 animals, and the data were averaged ± standard error. * Represents the significant difference from the control group at p<0.05

a represents a significant difference from the copper sulphate group

b represents a significant difference for the CO Q-10 group

c represents a significant difference for the CUSO4 with Q-10 group

TABLE 3. The level of caspase-3 in brain and liver tissue of chicks treated with copper sulfate and Q-10 at different times.

Parameters	Caspase-3 activity	Caspase-3 activity
	In liver tissue	In brain tissue
Control	0.036 ±0.001	0.044 ± 0.001
CuSO ₄	0.189 ± 0.002 [*]	0.173 ± 0.001 [*]
CO Q-10	±0.001 0.098	0.053 ± 0.0001
Q-10 with CuSO ₄	0.191 ±0.002	0.166 ±0.002
Q-10 before CuSO ₄	0.191 ±0.005 [*]	0.172 ±0.003 [*]
CuSO ₄ after Q-10	0.133 ±0.001 [*]	0.136 ±0.020 [*]

Each group of 6 chicks, the values represented average ± standard error

*Represents a significant difference from the control group.

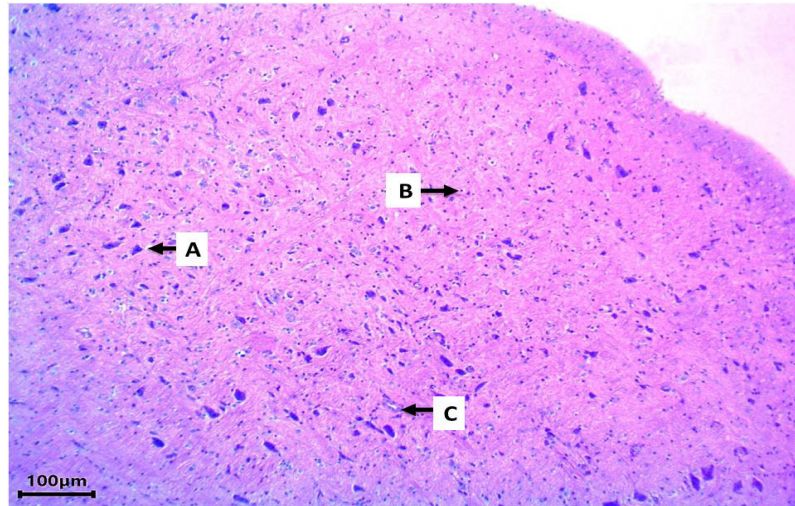


Fig. 1. Photomicrograph of brain for control group appeared the cortex of cerebrum in (normal architecture) neurons (A), glial cells (B) and, blood vessels (C). H&E stain.

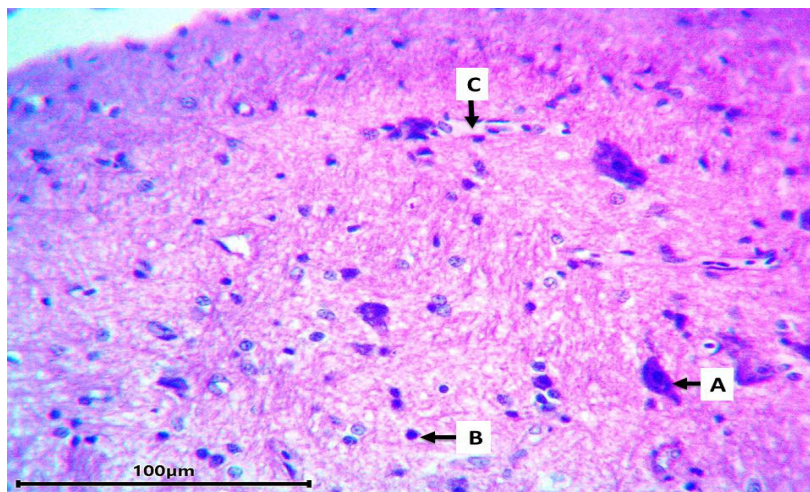


Fig. 2. Photomicrograph of brain for control group appeared the cortex of cerebrum in (normal architecture) neurons (A), glial cells (B) and, blood vessels (C). H&E stain.

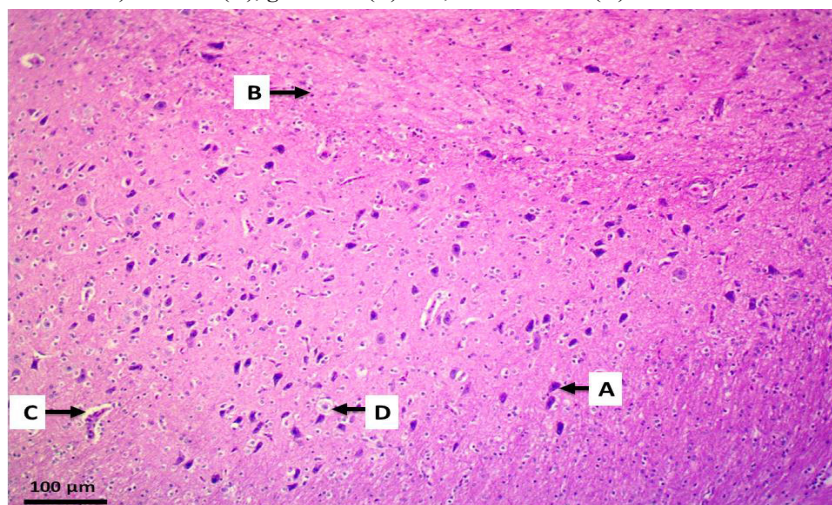


Fig. 3. Photomicrograph of chick brain of copper sulfate with Q-10 enzyme treated (G2) group shows the cortex of cerebrum with normal architecture representing by neurons (A), glial cells (B), mild perivascular (C) and Periaxonal edema (D). H&E stain, 100X.

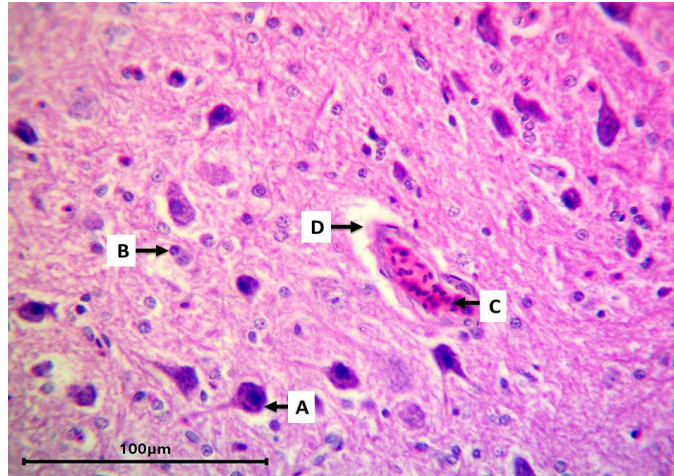


Fig. 4. Photomicrograph of chick brain of copper sulfate with Q-10 enzyme treated (G2) group shows the cortex of cerebrum with normal architecture representing by neurons (A), glial cells (B), congestion of blood vessels (C) and mild perivascular edema (D). H&E stain, 400X.

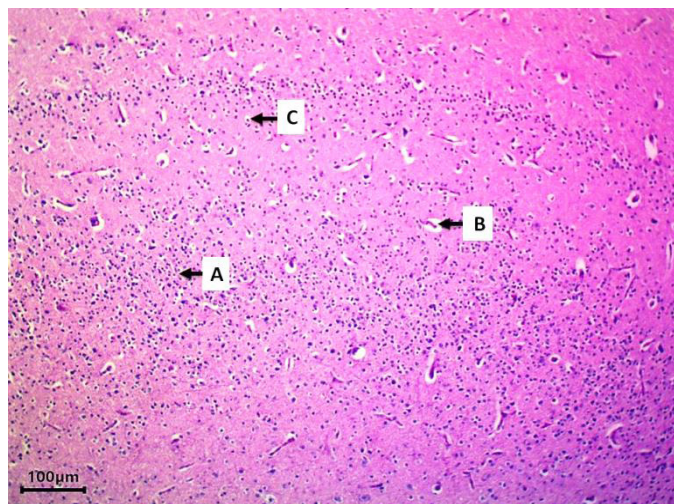


Fig. 5. Photomicrograph of chick brain of copper sulfate then Q-10 enzyme treated (G3) group shows the cortex of cerebrum with gliosis (A), diffuse perivascular (B) and periaxonal edema (C). H&E stain, 100X.



Fig. 6. Photomicrograph of chick brain of copper sulfate then Q-10 enzyme treated (G3) group shows the cortex of cerebrum with gliosis (A), diffuse perivascular (B) and periaxonal edema (C) Vacuolization of glial cells (D). H&E stain, 400X.

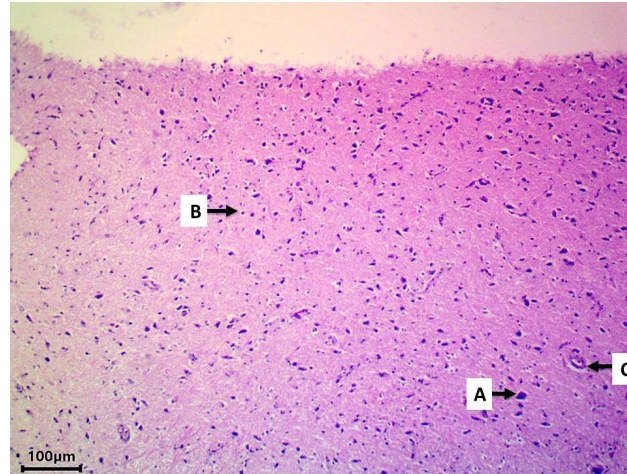


Fig. 7. Photomicrograph of chick brain of Q-10 enzyme treated (G4) group shows the cortex of cerebrum with normal architecture of neurons (A), glial cells (B), and blood vessels (C). H&E stain, 100X.

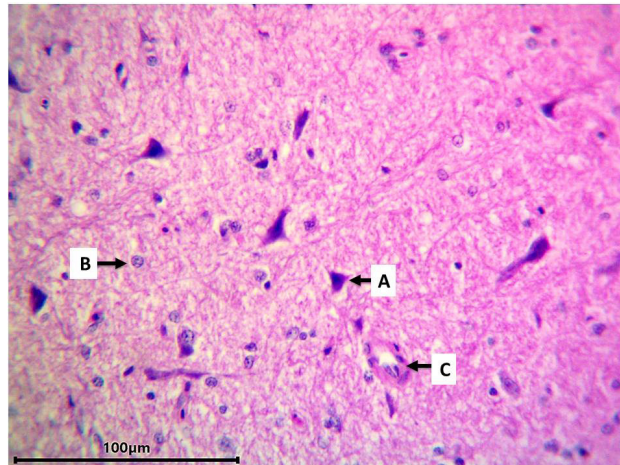


Fig. 8. Photomicrograph of chick brain of Q-10 enzyme treated (G4) group shows the cortex of cerebrum with normal architecture of neurons (A), glial cells (B), and blood vessels (C). H&E stain, 400X.

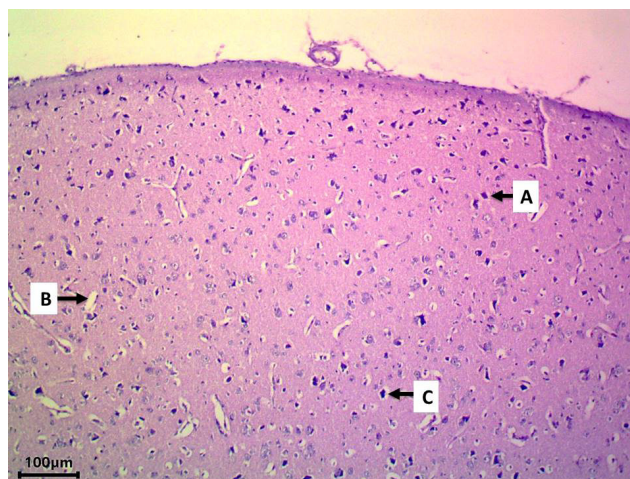


Fig. 9. Photomicrograph of chick brain of Q-10 enzyme then copper sulfate treated (G5) group shows the cortex of cerebrum with normal architecture of neurons (A) with mild perivascular (C) and Periaxonal edema (D). H&E stain, 100X.

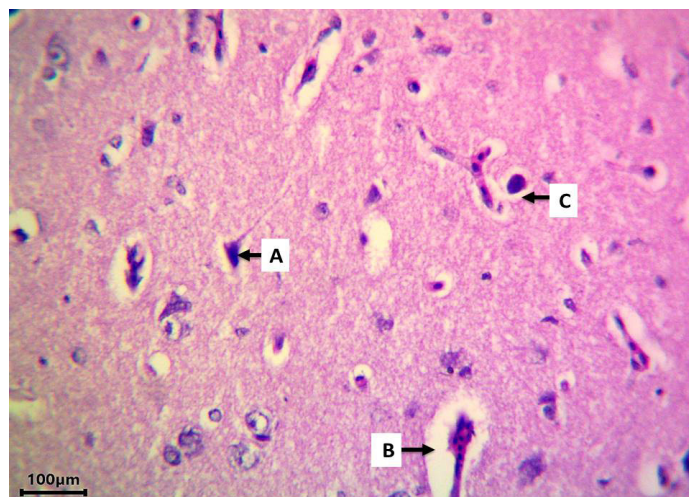


Fig. 10. Photomicrograph of chick brain of Q-10 enzyme then copper sulfate treated (G5) group shows the cortex of cerebrum with normal architecture of neurons (A) with mild perivascular (C) and Periaxonal edema (D). H&E stain, 400X.

Conclusion

This study found that giving the CO Q10 supplement with copper sulphate in the same time or before it reduced the harmful effects of copper sulphate, as seen by biochemical alterations, histopathological changes, and programmed cell death (apoptosis) in brain cells.

Acknowledgement

Thanks and gratitude to the College of Veterinary Medicine for all the facilities they provided to complete the research.

Conflict of interest

There is no conflict of interest.

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دور المساعد الانزيمي Co Q10 في سمية كبريتات النحاس في نموذج افراخ الدجاج

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استهدفنا معرفة قدرة الإنزيم المساعد Q-10 على مواجهة الضرر الناتج عن التسمم بكبريتات النحاس ، على مستويات التحدي الدوائي في الجهاز العصبي ، والإجهاد التأكسدي وبعض المتغيرات البيوكيميائية ، وكذلك دراسة التغيرات النسيجية المرضية في الدماغ. تم تقسيم ٧٢ فرخا عشوائياً إلى ٦ مجاميع كل منها مكونة من ١٢ فرخ. تم إعطاء الماء المقطر لوحده لمجموعة السيطرة G1 وأعطيت كبريتات النحاس وحدها بجرعة ١٩.٥ مجم /كجم لمدة ٣ أيام لمجموعة G2, ولمدة ٧ أيام أعطيت المجموعة G3 ٣٠مجم/كجم من CO Q-10 وحده, وأعطيت المجموعة G4 كبريتات النحاس لمدة ٣ أيام و Q-10 لمدة ٧ أيام. أعطيت المجموعة G5 كبريتات النحاس لمدة ٣ أيام قبل تلقي Q-10 لمدة ٧ أيام, وأعطيت المجموعة G6 المساعد الانزيمي Q-10 وحده لمدة ٧ أيام قبل إعطائها كبريتات النحاس لمدة ٣ أيام. كشف التحدي الدوائي عن اختلافات جوهرية في بداية النوم ومدة النوم في الافراخ عند إعطاء الإنزيم المساعد Q-10 مع كبريتات النحاس في أوقات مختلفة. تم ربط الإجهاد التأكسدي الكلي ، الكلوتاتيون ، والمالونديالديهيد في المصل وأنسجة الدماغ أيضاً بزيادة نشاط كاسبيس-٣ في أنسجة الدماغ ، في حين أن المجاميع التي تلقت المساعد الانزيمي Q-10 مع كبريتات النحاس بشكل متزامن أو قبل الإجهاد التأكسدي كانت أقل إجهاداً تأكسدياً و تعبيرات نسيجية مرضية أقل في أنسجة الدماغ. خلصنا إلى أن إعطاء Co Q-10 في نفس الوقت أو قبل كبريتات النحاس يقلل من سمية كبريتات النحاس وقد تم استخدام بعض علامات الإجهاد التأكسدي ، وكذلك المؤشرات الكيميائية الحيوية ، والتشوهات النسيجية المرضية ، والموت المبرمج في خلايا الدماغ ، لإثبات ذلك.

الكلمات المفتاحية: المساعد الانزيمي Q-10 , كبريتات النحاس, كاسبيس-٣ , الاجهاد التأكسدي, افراخ الدجاج